FDA DOCUMENTS

Endocrinologic and Metabolic Drugs Advisory Committee #72

Food and Drug Administration
Center for Drug Evaluation and Research

Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda MD

March 26, 1999

To discuss experience since approval for marketing, benefits, and risks of Rezulin™, (troglitazone, Parke-Davis Pharmaceutical Research, a Division of Warner-Lambert) and NDA 20 720; S12 for triple therapy with sulfonylurea and metformin in treatment of type 2 diabetes mellitus

Contents

Last negotiated draft
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Agenda

8:00 Call to Order, Introductions, Opening Comments:
Henry G. Bone III, M.D., Chair
Endocrinologic and Metabolic Drugs Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee
8:10 Background and Purpose:
James Bilstad, M.D., Director, Office of Drug Evaluation II

8:20 Open Public Hearing
9:20 Sidney M. Wolfe, M.D., Director, **Public Citizens Health Research Group**
9:30 **American Diabetes Association**

9:40 FDA: Epidemiology and Hepatotoxicity: David J. Graham, MD, MPH
Office of Postmarketing Drug Risk Assessment

10:45 Break

11:00 Parke-Davis: Epidemiology and Hepatotoxicity:

12:00 Lunch

12:45 Parke-Davis: Overall Efficacy, Triple Therapy, Summary Statement
1:30 Discussion
2:30 Charge to the Committee, Introduction to Questions:
James Bilstad, M.D., Director, Office of Drug Evaluation II
2:45 Questions
Break
5:00 Adjourn

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Proposed Questions

1. **Based on the available information, with the currently labeled indications, (including the proposed triple therapy) warnings and precautions, do the benefits of troglitazone therapy outweigh its risks?**

2. **If the answer to Q1 is yes, can the current labeling be enhanced to further improve the risk/benefit relationship?**

   How?

   What other steps should be taken?

3. **If the answer to Q1 is no, could modification of the current labeling result in a favorable risk/benefit ratio?**

   What changes are recommended?

   What additional steps should be taken?

4. **Is any additional information recommended concerning the hepatic effect of troglitazone?**

NDA 20-720

Troglitazone – Efficacy Supplement

Submitted November 18, 1998

Reviewed by Robert I Misbin MD
March 12, 1999

INTRODUCTION:

Troglitazone is currently approved for treatment of type 2 diabetes as monotherapy or in combination with insulin or sulfonylureas. This review deals with an efficacy supplement that contained a new study showing that troglitazone improves hyperglycemia in patients inadequately treated with sulfonylureas plus metformin, protocol 991-105. Other new data submitted regarding other aspects of troglitazone treatment are discussed. These include a comparison of troglitazone, monotherapy and the combination, protocol 991-075, a comparison of troglitazone and metformin monotherapy (Glaxo 3002), and a study of the effects of troglitazone on body composition, protocol 2019. There is no new safety information except as noted. I also give a brief chronology of the development of liver failure in patients on troglitazone with details of findings of transaminase elevations that occurred during the clinical trials. A discussion of the post-marketing cases of liver failure will be presented to the Endocrine and Metabolic Advisory Committee by Dr David Graham on March 26, 1999.

REVIEW OF HEPATOTOXICITY

Mean transaminase levels fell in patients treated with troglitazone in phase 3 trials, probably reflecting improvement in steatosis that is frequently present in livers of patients with poorly controlled diabetes. One patient had a baseline ALT elevation of 148 U/l which normalized to 18 U/l on troglitazone. A second patient had a baseline elevation of 98 which fell to 53 on troglitazone.

The initial labeling for troglitazone contained information about two patients* who developed reversible jaundice during the trials and had biopsy findings of "idiosyncratic drug reaction." It was also stated that 2.2% of patients during the trials had a transaminase (ALT or AST) level exceeding 3xULN. In many of these patients, ALT levels fell despite continuation of troglitazone treatment. With only two cases of jaundice in a database of over 2500 patients, it was not apparent that routine liver monitoring would have been productive. As noted above, ALT elevation due to diabetes itself appeared to be improved by troglitiazone. Since the treatment-emergent elevation was reversible in all cases, inclusion of the data mentioned above in the warnings and laboratory abnormalities sections was thought to have been adequate.

What was not appreciated by DMEDP was that many of the patients classified as ALT > 3xULN actually had ALT values that were VERY much greater than 3xULN.

The first cases of frank liver failure related to troglitazone surfaced in October 1997, and required a reassessment of the data from the clinical trials. On October 21, 1997, Parke Davis submitted a document to their IND summarizing the experience regarding abnormal liver tests from the clinical trials based on information available through February 1, 1997. These data are summarized in the table below. Of patients with treatment emergent ALT values >3x ULN, the median study duration to peak ALT elevation was 121 days. There were 24 patients in whom troglitazone was discontinued because of an ALT elevation. In reviewing these data, I believe that one of these cases could be explained by preexisting elevation . 22 of the remaining 23 patients had treatment-emergent ALT values over 3x ULN. The highest baseline value was 65 U/L (1.9 x ULN) In 14 of these 23 patients, the ALT value exceeded 8xULN (272 U/L based on normal ALT up to 34 U/L) and in 5/23 patients the ALT value exceeded 30xULN.. There were also 17 patients who developed ALT elevation > 3x ULN while on troglitazone in whom the abnormality reversed despite continuation of troglitazone. In 5 of these patients, ALT exceeded 8xULN. The highest value was 12 xULN. There were additionally 8 patients with ALT > 3xULN with elevations that persisted at the end of the trial but whose ALT normalized following completion of troglitazone treatment. ALT elevations appeared to occur more frequently in the Glyburide add-on trial than in the other trials. Among 237 patients treated with troglitazone plus glyburide, six patients were withdrawn because of ALT elevations and five patients had ALT elevation that normalized despite continued treatment. Among 236 patients on troglitazone alone, one was withdrawn because an ALT elevation, three normalized despite continued treatment, and two normalized after troglitazone was withdrawn. The total number of patients was 11 /237 (4.6%) for glyburide plus troglitazone and 6/236(2.5%) for troglitazone alone. Before concluding that glyburide may increase the risk of hepatic toxicity due to troglitazone, one must assess possible differences in the length of exposure. This trial was a 12 month comparison of troglitazone plus glyburide to troglitazone alone. Although equal numbers of patients were randomized to troglitazone plus glyburide (n=237) as troglitazone alone (n= 236), the dropout rate due to lack of efficacy was very high for patients on troglitazone alone. 90 patients on troglitazone alone completed the study compared to 180 patients on troglitazone plus glyburide. The troglitazone vs placebo trials only lasted six months, and were also associated with a high drop-out rate because of lack of efficacy. Thus, part of the apparent increase in troglitazone hepatotoxicty in patients on glyburide may be due to longer exposure. On the other hand, it should be noted that only 3 of the 11 patients on glyburide plus troglitazone and 1 of the 6 patients on troglitazone alone had their ALT elevation after 180 days.

Some of the data, which Parke Davis submitted on October 21, 1997, appeared inconsistent with the section on "abnormal liver function tests" in the text of the safety update of May 21, 1997 which Parke-Davis submitted prior to approval of the efficacy supplements for monotherapy and the combination of troglitazone with sulfonylureas. In response to a request for clarification, Parke Davis explained that two patients mistakenly described in the safety update as having ALT values <3xULN actually had values >3xULN. One of these had an ALT of 1111. In addition, PD explained that the discussion of patients with elevated ALT levels in the text of the safety update pertained to patients reported as "elevated ALT levels" as the COSTART term. Patients were apparently not included in this section if the COSTART term was "liver function test abnormal".

NDA Data base
ALT Elevations during Clinical Trials

ALT max	Continued on drug Value at end of trial		Withdrawn	Total
	Normal	Abnormal**		
>3 xULN (102 U.L)	17	8	23	48 (1.9%)
>5xULN (140 U/L)	16	6	20	42 (1.7%)
>8xULN (270 U/L)	5	3	14	22 (0.9%)
>30xULN (1020U/L)	----	---	5*	5* (0.2%)

Data from submission to IND October 21, 1997 * 2 jaundiced
Upper limit of normal taken as 34U/L ** normalized following drug withdrawal
N= 2510 (n= 1715, 3 months of longer)

It is worthy of note that the incidence of abnormal ALT values in the NIH diabetes prevention trial terminated in June 1998 appears somewhat higher than that shown in the table above. Of 585 patients on troglitazone, 18 patients (3.0%) had an ALT value over 3x ULN. In 9 patients (1.5%), it exceeded 8xULN. Two patients had ALT values over 30 x ULN. One of these patients developed liver failure and was given a transplant but died soon after. The second patient recovered. The median duration of troglitazone treatment to initial ALT elevation was 126 days and to peak elevation was 143 days. The highest initial ALT value for any of these patients was 0.6 x ULN.

The incidence of 3.0% for ALT > 3x ULN in the NIH trial appears higher than the 1.9% found in the NDA database. The incidence of ALT values > 30x ULN was 0.2% (5/2510) in the NDA data base and 0.3% (2/585) in the NIH study. These apparent differences may possibly be explained by the fact that about 800 patients in the NDA database had been exposed to troglitazone for less than three months and therefore were not as vulnerable to liver damage as patients who had been exposed longer. Another difference is that the ULN for ALT was adjusted for age and sex in the NIH report.

Since the first cases of liver failure which surfaced in fall 1997, DMEDP has taken the position that Rezulin could be used safely provided that patients were monitored for early signs of liver damage. In July 1998, monthly monitoring was added to the label to try to prevent the rapid development of irreversible liver damage that occurred in the patient in the NIH diabetes prevention trial It has recently become apparent, however, that even monthly monitoring will not prevent every case. In January 1998, we became aware of a 63 year old patient in a Parke-Davis postmarketing study who developed irreversible liver damage 41 days after starting Rezulin. Her ALT had been normal at baseline (17) and had been normal (22) just 13 days before the ALT value of 1130. She then went on to develop liver failure and died several weeks later. That this happened in one of Parke-Davis' own studies is evidence that the safety of troglitazone cannot be assured., even with monthly monitoring of liver enzymes.

In the clinical trials which led to troglitazone's approval, there were no cases of liver failure in 2510 patients (NDA data base in previous table). Now we have one death due to liver failure in a postmarketing study of about 2500. We also know of one liver transplant among the 585 patients exposed to troglitazone in the NIH diabetes prevention trial. Combining the NDA data base and the NIH trial, there were 7 patients out of 3095 (six in addition to the one liver transplant patients in the NIH trial) whose ALT value exceeded 30 x ULN, an elevation which most clinicians would consider to be dangerous. Although the numbers are too small to be confident about calculating an incidence rate, it is hard to deny that these cases create a serious doubt about the safety of troglitazone. By contrast, I am not aware of a single case of lactic acidosis, let alone a death due to lactic acidosis, in over 6,000 patients who have received metformin in clinical trials. The fact that liver failure due to troglitazone cannot always be prevented, even with monthly monitoring, requires that we redefine the patient population for which troglitazone is really needed.

*Two patients had liver biopsies showing idiosyncratic drug reaction, but only one of these patients was jaundiced. An additional patient had jaundice believed to be due to recent exposure to an environmental toxin. This error was corrected in a subsequent label.

LABELING:

Liver injury: There is now enough information about liver injury that the terms "rare" and "very rare" seem inappropriate. Classifying cases as "ALT levels greater than 3x ULN" also serves to understate the problem.

I would suggest the following language:

> WARNING: Rezulin can cause severe idiopathic hepatocullar injury. This injury is usually reversible but can cause liver failure even if Rezulin is discontinued. The injury typically occurs between one month and eight months after treatment is started.

I would also expand the section about the clinical trials in the boxed warning:

> There were 48 patients with ALT values over 3 x ULN. 22 patients had ALT values over 8 x ULN. 5 patients had ALT values over 30x ULN. Total exposure was 2510 patients of whom 1715 received troglitazone for three months or longer. The median duration of treatment to peak ALT level was 121 days

Mechanism of action: The paragraph dealing with islet function should be omitted. Improvement in beta cell function in troglitazone-treated patients is probably a non-specific finding related to improvement in hyperglycemia.

Clinical effects: The addition of new information about lipids can be added as written, but a statement should be included indicating that the clinical significance of these lipid changes is not known.

Combination with SFU: The new paragraph dealing with body distribution should be deleted. This was from a small study with incomplete data in which troglitazone was not very effective.

Monotherapy: . The response rate, based on reduction in FPG of >30 mg/dl is only about 50%.

RECOMMENDATIONS:

Combination therapy:

Troglitazone is highly effective in patients with type 2 diabetes whose hyperglycemia is resistant to insulin treatment. These patients tend to be older than patients who do not require insulin. They are also more likely to have the kidney and heart involvement that would increase the risk of lactic acidosis if they were treated with metformin.

This submission provides strong evidence for the labeling claim that troglitazone is effective when added to patients inadequately controlled on a combination of a sulfonylurea plus metformin. These three classes of drugs work through largely different mechanisms so that triple drug combination therapy makes a good deal of sense

Monotherapy:

text redacted
3/12/99

Robert I Misbin MD
DEMPD
HFD 510/misbin/sobel/malozowski
March 12, 1999

Epidemiology of Hepatoxicity with Troglitazone

David J. Graham, MD, MPH
Lanh Green, RPh, MPH

Office of Postmarketing Drug
Risk Assessment
Center for Drug Evaluation and Research

Background Information on Acute Liver Failure

Definitions of Acute Liver Failure

- Trey and Davidson (1970):
  - Encephalopathy within 8 weeks of first symptoms of illness; in the absence of pre-existing liver disease
- Bernuau, et al. (1986):
  - Encephalopathy within 2 weeks (fulminant) of up to 12 weeks (subfulminant) following the onset of jaundice; in the absence of pre-existing symptomatic liver disease
- O'Grady, et al. (1993):
  - Encephalopathy within 1 week (hyperacute) or 4 weeks (acute) or 12 weeks (subacute) following onset of jaundice; in the absence of pre-existing symptomatic liver disease

Proposed Classification Systems for Acute Liver Failure

UK (King's College, London)	
Hyperacute	0-7 d
Acute	8-28 d
Subacute	29-84 or 182 d

France (Hopital Beujon, Clichy)	
Fulminant	0-14 d
Subfulminant	15-84 d

United States	
Fulminant	0-56 d
Subfulminant	57-182 d

Criteria for Grading the Level of Hepatic Encephalopathy

- Grade 1 Mild confusion; slowed mentation
- Grade 2 Drowsiness; inappropriateness; asterixis
- Grade 3 Sleepy but rousable; incoherent speech; marked confusion
- Grade 4 Comatose; A: responds to pain
  B: no response to pain

Clinical Features of Acute Liver Failure

- Hepatic encephalopathy
- Coagulopathy
  - Platelets
  - PT
- Renal Failure
- Cardiac
  - Hypovolemia
  - High CO
- Metabolic
  - Hypoglycemia
  - Lactic acidosis
  - Electrolytes
- Sepsis

Pathophysiology of Acute Liver Failure

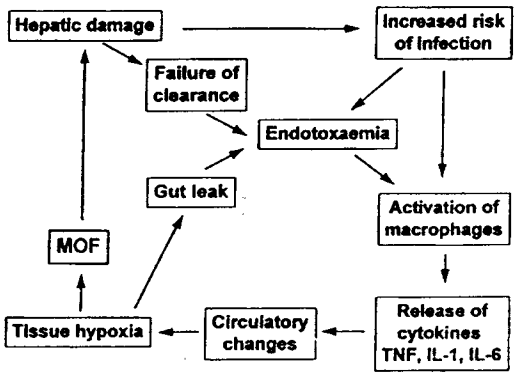


FIG. 1. Vicious cycle of events in pathogenesis and basis of multiorgan failure (MOF).

Semin Liver Dis 1996;16:343-8

Etiology of Acute Liver Failure

	UK	France	US
Viral	34%	72%	70%
Acetaminophen	57%	2%	15%
Drug	3%	15%	10%
Others	6%	11%	5%

Etiology of Acute Liver Failure by Time of Onset, UK

	Hyperacute (n=81) %	Acute (n=89) %	Subacute (n=59) %
HAV	19.8	10.3	6.8
HBV	37.0	16.0	6.8
NANB	17.3	45.3	83.0
Inc serology	18.5	18.1	-
Halothane	1.2	4.5	-
Drugs	6.2	6.8	3.4
Cereb edema	69.0	56.0	14.0
Survival w/o Tx	36.0	7.0	14.0

Lancet 1993;342:273-5

Mortality Rates from Acute Liver Failure (Pre-Transplant)

	Mortality	
Cause of ALF	Italy	UK
HAV	50-60%	33%
HBV	65-80%	61%
NANB	90%	80%
Drug	90%	88%

Survival Rates from Acute Liver Failure including Transplantation

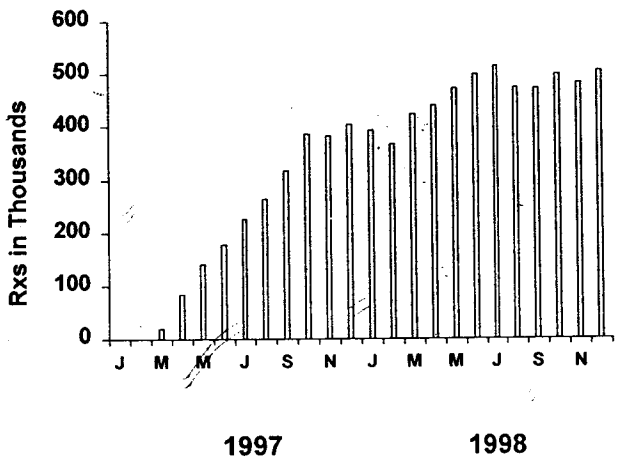
	Survival
Cerebral edema	
Absent	67%
Present	50%
Cerebral edema and oliguric renal failure	30%

Summary of Outcome of Acute Liver Failure from Five Liver Transplant Centers in the US, 1984-1996

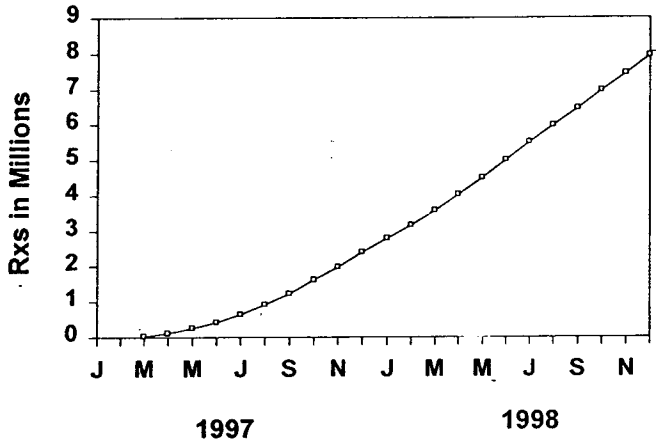
	Number (%)
Alive	
No transplant	50 (23.5)
Transplant	77 (36.2)
Dead	
No transplant	54 (25.4)
Transplant	32 (15.0)

Troglitazone Drug Usage Data

Monthly Prescriptions of Troglitazone in the US, 1997-1998, NPA™ Data



Cumulative Prescriptions for Troglitazone by Month in the US, 1997-1998, NPA™ Data

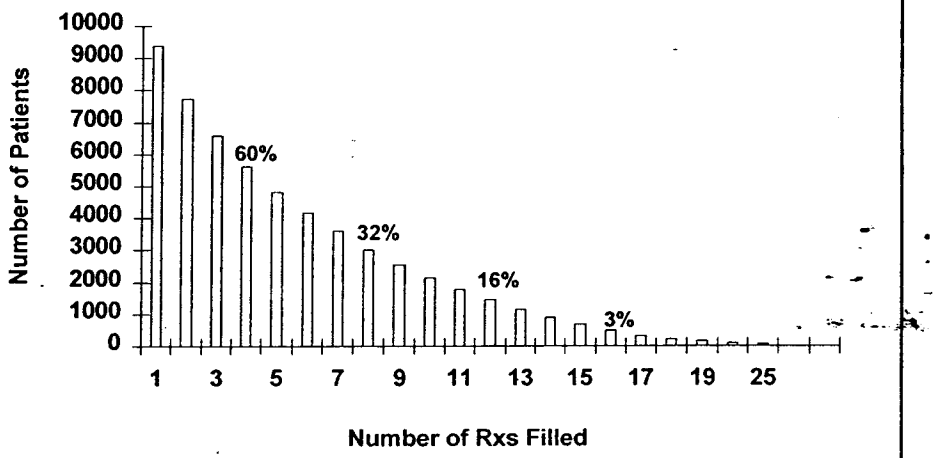


Troglitazone Use in the US, NDTI™, 1997-1998

% Female	43%
Mean Age	60.7

Age Distribution	% Total
0-34	2.2
35-44	8.9
45-54	19.4
55-64	28.3
65+	41.1

Continuation of Troglitazone Use by Patients Treated with the Drug, UHC, 1997-1998



Review of Reported Cases of Acute Liver Failure and Hepatitis with Troglitazone

Definitions Used to Classify Case Reports - 1

- Acute Liver Failure
  - Used classification scheme by O'Grady, et al (UK, 1993)
  - Measured the interval from jaundice onset to encephalopathy/ transplant or death (variable named JENTD in subsequent slides)
  - If timing of jaundice unknown, used time of onset of other symptoms, or of stopping troglitazone use

Definitions Used to Classify Case Reports - 2

- Rapid Riser
  - Patient in whom markedly abnormal liver tests were obtained within "a month" of previously normal test results
- Unknown Riser
  - Patient in whom the time course of development of abnormal liver tests is unknown

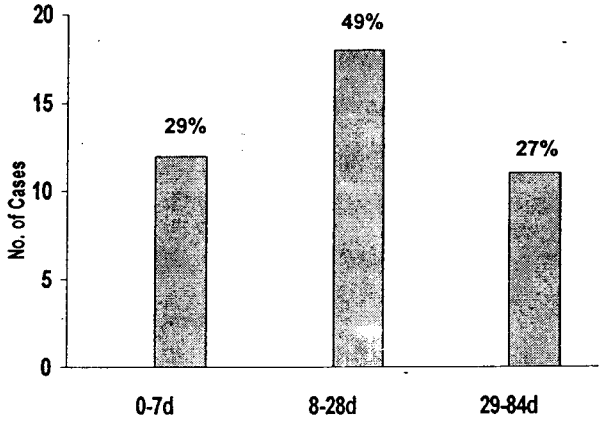
Overview of Reported Cases of Hepatitis and Acute Liver Failure with Troglitazone

Hepatitis	81
Not hospitalized	29
Hospitalized	46
Unknown	6
Acute Liver Failure	43
Probable	38
Possible	5

Outcome in 43 Reported Cases of Acute Liver Failure with Troglitazone

Alive	12	(27.9%)
No transplant	5	
Transplant	7	
Dead	28	(65.1%)
No Transplant	26	
Transplant	2	
Unknown	3	(7.0%)

Timing of Onset of Acute Liver Failure in 43 Reported Cases

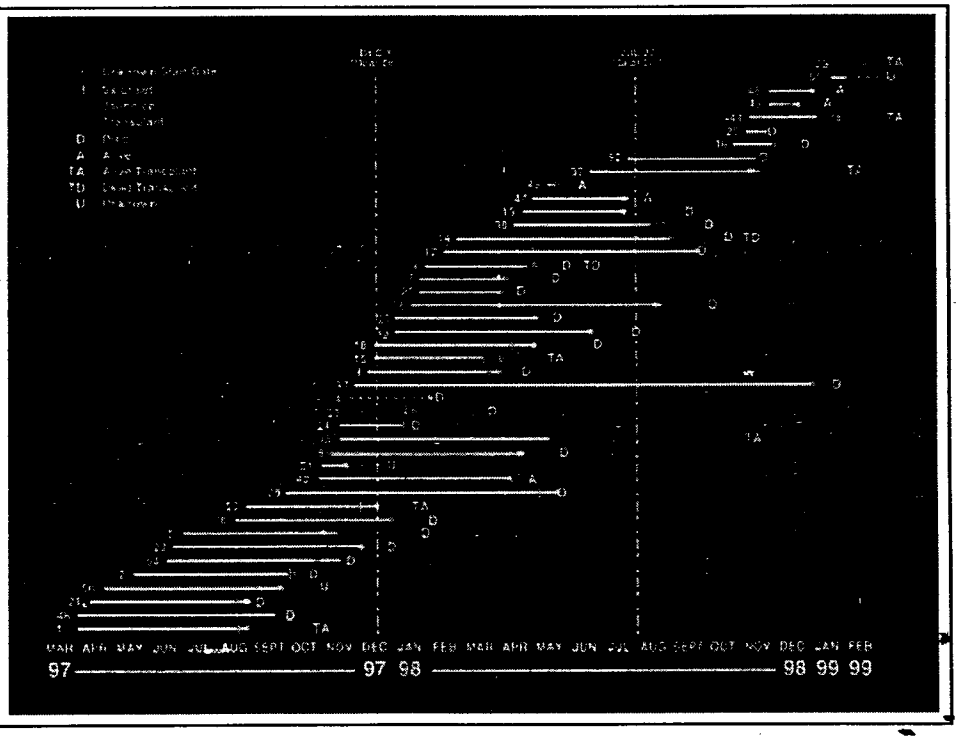


Patient Characteristics in 43 Reported Cases of Acute Liver Failure with Troglitazone

Female		69.8%	
Age		63.3	(43-91)
Duration of Rx		134 d	(4-478)
Daily dose	200mg	20.0%	
	400mg	68.6%	
	600mg	11.4%	
Jaundice as 1st Sx		62.2%	
Jaundice @ Dx		89.2%	
Time from jaundice to encephalopathy		19 d	(0-70)

First Indication of Hepatic Injury in 43 Reported Cases of Acute Liver Failure

Jaundice	23	(62.2%)
Other Sxs	9	(24.3%)
Unknown	(6)	



Relationship of Daily Troglitazone Dose and Outcome of Acute Liver Failure in 43 Reported Cases*

	Outcome	
Daily Dose	Alive	Dead
200 mg		7
400 mg	9	13
600 mg		4
Unknown	3	4

*3 Patients with outcome unknown

Liver Enzyme Monitoring in 43 Reported Cases of Acute Liver Failure

Baseline	20	46.5%
Monthly	8	18.6%
Rapid Riser	9	20.9%
Unknown Riser	31	72.1%

Comparison of Cases of Acute Liver Failure with Documented Rapid Rise in Liver Enzymes to Cases with Unknown Enzyme Timecourse*

	Rapid Riser (n=9)	Unknown Timecourse (n=31)
Age	67.2	61.9
% Female	66.7	67.7
Duration Rx (d)	134.1	138.4
Daily Dose (mg)	400.0	384.0
JENDT (d)	16.2	20.3
% Hyperacute	22.2	27.6
% Jaundice 1st	50.0	73.1

*No differences are statistically significant

Time-Course of Liver Enzyme Monitoring, Symptoms and Acute Liver Failure in a "Rapid Riser" Treated with Troglitazone - 1

	ALT	AST	AlkP	Tbili	
5Feb98	20	19	128		
11Feb98					Began troglit
7Aug98	32	30		0.6	
17Aug98			93	0.6	Some nausea
22Aug98	1670	1688		5.5	Jaundice, hosp
9Sep98					Enceph; intub
10Sep98					Liver tx
12Sep98					Death

Case 14

Time-Course of Liver Enzyme Monitoring, Symptoms and Acute Liver Failure in a "Rapid Riser" Treated with Troglitazone - 2

	ALT	AST	AlkP	Tbili	
14Dec97	14				Began troglit
9Feb98	15				
21Mar98	69				<1.5xULN
Mar/Apr					N/V/J
22Apr98	590	848	108	21	Stopped troglit; Hosp
30May98	373	910	198	25	Coag; enceph
19Jun98					Death

Case 18

Time-Course of Liver Enzyme Monitoring, Symptoms and Acute Liver Failure in an "Unknown Riser" Treated with Troglitazone - 1

	ALT	AST	AlkP	Tbili	
1Dec97					Began troglit
3Dec97	11				"Normal"
1Mar98					Anorexia
4Mar98	252		54	0.5	6xULN; stopped troglit
25Mar98	>1400				Jaundice
15Apr98					Enceph; stage III
18Apr98					Liver tx

Case 15

Time-Course of Liver Enzyme Monitoring, Symptoms and Acute Liver Failure in an "Unknown Riser" Treated with Troglitazone - 2

	ALT	AST	AlkP	Tbili	
28Nov97	14	12	69	0.6	Began troglit
20Jan98	47	30	48	0.5	
20Feb98					Skipped testing
20Mar98	3000	2940	167	11.2	Stopped troglit
7Apr98					Hepatic coma
13Apr98					Died

Case 3

Observations from Reported Cases of Acute Liver Failure in which Some Liver Enzyme Monitoring Occurred

- Restarting troglitazone after abnormal LFTs
- Time-lag between blood draw, test-results and communication with patient
- Fractionation of patent care
- Long prescriptions
- Continuing after onset symptoms (n/v)
- Miscommunication and lack of physician follow-up
- H/o prior transaminase elevations on lipid-lowering drugs
- Baseline < 1.5-2xULN
- Continuing after mild elevation noted (2.1xULN)
- Unawareness by physicians (ER example)

Summary From Review of Reported Acute Liver Failure Cases with Troglitazone - 1

- For most, the time course of liver enzyme changes is unknown (n=31).
- In 21% of all cases (75% of those with liver enzyme data within a monthly interval) the transition to irreversibility occurred within the month (range 4 - 34 days).

Summary From Review of Reported Acute Liver Failure Cases with Troglitazone - 2

- The question is, for the 72% of cases with unknown enzyme time course, does irreversibility occur quickly? Even for the 3 cases where enzyme increases were not rapid, we don't know when they became irreversible.
- The case with irreversibility when the ALT=252 highlights this issue.

Comparison of Troglitazone with Other Drugs

Reporting Rates to FDA of Serious Liver Injury with Selected Oral Hypoglycemic Agents

	Reporting Rates per 10^6 Rx		
	Sulfonylureas	Metformin	Troglitazone
Fatal			
All yrs	.05	.25	6.80
1st 3 yrs	.14	.26	6.80
Non-fatal			
All yrs	.04	.20	6.55
1st 3 yrs	.12	.17	6.55

Registration Rates for Liver Transplantation per 10^9 Prescriptions of Selected Drugs , UNOS, April 1994 - October 1998

Drug Group	No. Registered for LTx	Rxs in Millions	LTx Registration Rate per 10^9 Rxs (95% CI)
Sulfonylureas	0	166.3	0 (0-18)
Metformin	0	40.0	0 (0-75)
Troglitazone	3	7.9	378 (78-1100)
NSAIDS	6	372.1	16 (6-35)
Bromfenac	2	2.6	772 (94-2810)
HMG Co-A	1	206.1	5 (0.1-27)

Metformin and Lactic Acidosis - 1

- 1980-1995
- Saskatchewan, Canada
- 11,797 patients
- 22,296 person-years
- 10 persons with hosp dx "acidosis"
- 6 eliminated on review
- Authors included 2 in rate calculations because of increased lactate levels
- Rate of lactic acidosis 9 per 100,000 pyrs (0-21)
- Authors noted presence of other factors that could explain lactic acidosis

Metformin and Lactic Acidosis - 2

Two patients included in rate calculations

#1 60 M w/20 yr h/o EtOHism and liver disease
Adm w/ sepsis and hepatic encephalopathy
Lab error; spurious lactate level

	Adm	+2d	+3d
pH	7.25	7.53	7.50
Lactate		12	1.9

#8 83 F adm w/ necrotic bowel and sepsis; died
Blood lactate level 13.2 mmol/L

Metformin and Lactic Acidosis - 3

Two patients not included in rate calculation

#5 85 F adm w/ sepsis and renal failure

#9 72 F adm w/probable pulmonary edema, hypoxemia, CHF

	9:20p	11:30p	8:45a
pH	6.92	7.28	7.37

Metformin and Lactic Acidosis - 4

- Each of 4 patients with other conditions accounting for anion-gap acidoisis
  - Peripheral vasoconstriction
  - Hypoperfusion
  - Tissue hypoxia
  - Renal failure
  - Liver failure
  - Sepsis
- No cases with isolated metformin-induced lactic acidosis
- Rate: 0 per 10^5 pyrs (0-13.4)

Underreporting of Cases

Barriers to Reporting

- Diagnosis
- Recognition and attibution
- Registration

Underreporting of Adverse Drug Reactions From the Literature

Country	Drug	Reaction	Reporting Rate
UK	Practolol	Oculocutaneous syn	<< 2%
UK	NSAIDS	Aplastic anemia	11%
UK	OC's	TE death in women	15%
US	Digitalis	Hosp for toxicity	0.3%
US	Isoniazid	Fatal hepatitis	10%
US	DTP	SIDS	10-20%
US	RI survey	Serious	<< 3%
US	MD survey	Medically serious	< 8-13%

Attribution of Acute Liver Failure to Drug Exposure From the Literature

	Attribution Rate
Fatal INH hepatitis	26%
Idiopathic hospitalized hepatitis	25%

Background Rates for Drug-Induced Hepatitis and Acute Liver Failure

Epidemiologic Studies Providing Population Estimates of Hospitalization for Acute Drug-Associated Hepatitis

Country	Source	Years	Person-Years	Rate per 10^5 Person Years (95% CI)
Denmark	Registry	1981-85	25.5×10^6	2.0 (1.8 – 2.2)
U.S.	Medicaid	1980-87	9.8×10^6	2.2 (2.0 – 2.4)
U.S.	HMO	1977-81	1.4×10^6	0.9 (0.4 – 1.5)
Canada	SPDP	1982-86	0.47×10^6	3.9 (2.3 – 6.1)
U.K.	GPRD	1987-91	0.18×10^6	<2.2 (0.6 – 5.6)
U.S.	HMO	1989	0.07×10^6	0 (0 – 5.2)

Epidemiologic Studies Providing Population-Based Estimates of Acute Liver Failure

Country	Source	Years	Person-Years	Rate per 10^6 Person Years (95% CI)
U.S.	Medicaid	1980-87	9.8×10^6	0.8 (0.3 – 1.6)
U.S.	HMO	1977-81	1.4×10^6	0 (0 – 2.6)
Canada	Saskatch	1982-86	0.47×10^6	0 (0 – 6.4)
U.K.	GPRD	1987-91	0.26×10^6	0 (0 – 11.7)
U.K.	GPRD	1990-93	0.18×10^6	0 (0.6 – 16.6)
			12.11×10^6	0.6 (0.2 – 1.3)

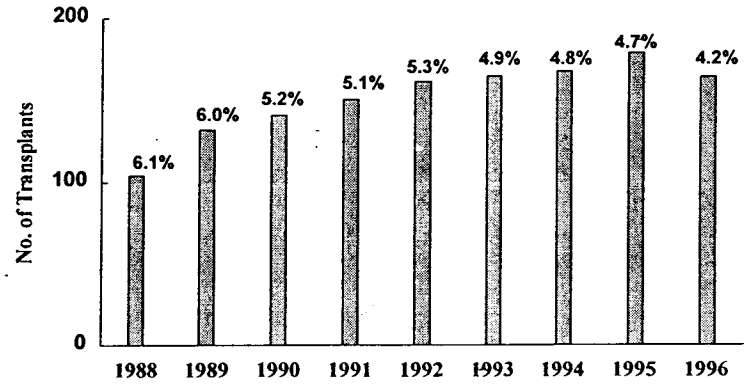
U.S. Liver Transplant Rates in Adults, 1987-1995, UNOS and U.S. Census Data

	Rate per 10^6 pyrs	
Cholestatic cirrhosis	2.24	
Other cirrhosis	7.00	
Acute hepatic necrosis	0.66	
Viral	0.34	(51.6%)
Drug /Toxin	0.11	(16.7%)
Unspecified	0.21	(31.7%)
Other	0.02	(3.3%)
Metabolic	0.43	
Malignancy	0.45	
Benign neoplasm	0.06	
Miscellaneous	0.17	
Overall	11.04	

Liver Transplant Rates by Year for Acute Liver Failure in Adults, UNOS, 1987-1995

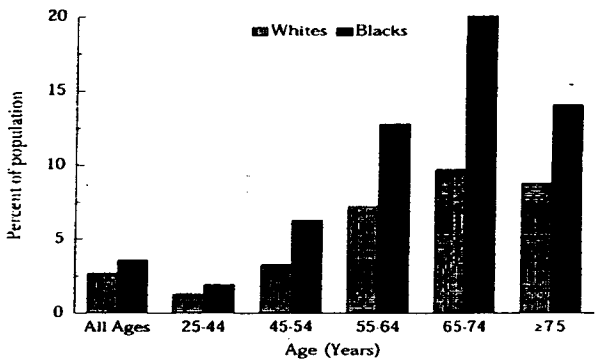
	Rates per 10^6 pyrs		
	AHN	Unspecified	Drug/Toxin
1991	.568	.232	.062
1992	.644	.317	.107
1993	.728	.263	.157
1994	.846	.326	.115
1995	.838	.228	.119
1987-95	.664	.119	.105

Trends in Transplant of Adults for Acute Hepatic Necrosis in the US, 1988-1996, UNOS



Diabetes and Acute Liver Failure

Figure 4.5
Percent of Whites and Blacks with Diagnosed Diabetes, by Age, U.S., 1990-92



Source: Unpublished analyses of the 1990-92 National Health Interview Surveys

Chap 4, Diabetes in America, 2nd ed, 1995

Percent of Whites and Blacks with Diagnosed Diabetes, by Age, NHIS, 1990-92

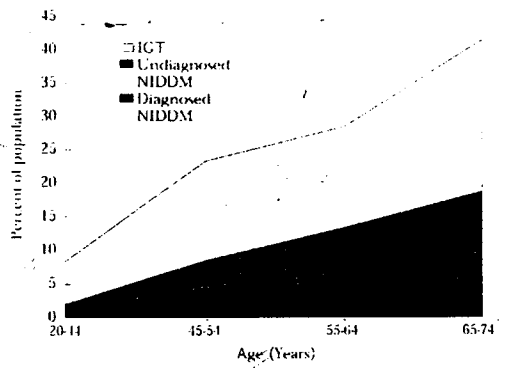
	White	Black
25-44	1.5	2.0
45-54	3.0	6.5
55-64	7.5	13.0
65-74	10.0	20.0

Percent of US Population with Diagnosed Diabetes, by Age, 1991-93

< 45	1.0%
45-64	5.9%
65-74	10.5%

National Health Information Survey
Chap 4, Diabetes in America, 2nd ed, 1995

Prevalence of Undiagnosed and Diagnosed Diabetes and IGT in the U.S. Population, 1976-80



IGT, impaired glucose tolerance.

Source: Reference 2, 1976-80 Second National Health and Nutrition Examination Survey

Chap 4, Diabetes in America, 2nd ed, 1995

Data from United Network for Organ Sharing (UNOS)

- Data to be presented

Modeling of Risk and Hazard Rates for Acute Liver Failure with Troglitazone

Methods Used to Estimate the Risk of Acute Liver Failure in Patients Treated with Troglitazone - 1

- Standard life-table analysis
- Used pattern of troglitazone use from UHC database to estimate national patterns of usage
- Calculated the rate of acute liver failure for each separate month of drug usage (interval-specfic hazard rate)

Methods Used to Estimate the Risk of Acute Liver Failure in Patients Treated with Troglitazone - 2

- Calculated the cumulative risk of acute liver failure experienced by each individual completing a given number of months of troglitazone use
- Presented analyses adjusted for underreporting of cases

United HealthCare Research Databases

- National healthcare management company providing medical health insurance coverage to > 13 million people, primarily through Independent Practice Association model networks
- Research database covers 3.5 million people in 12 separate health plans located in 9 separate states
- Computerized data on prescription drugs; outpatient and inpatient diagnoses and procedures; laboratory tests (but not actual lab results); other

Life-Table Analysis of Risk of Acute Liver Failure with Troglitazone Based on Spontaneously Reported Cases from an Estimated Population of 1.23 Million Users, 1997-1998

Months of Use	Interval Specific Hazard Rate per 10^6 pyrs	Cumulative Risk (1 per "X" Users)
1	56	209,158
2	40	121,886
3	46	82,237
4	106	47,129
5	162	28,566
6	185	19,700
7	54	18,076
8	94	15,788
9		
10		
11		
12		
13		
14	96	13,977
15		
16	185	11,451

Cumulative Risk of Acute Liver Failure in Patients Treated with Troglitazone by Duration of Use, Adjusting for Underreporting*

Duration of Use	Level of Underreporting 25%	10%	5%
1 mos	52,290	20,916	10,458
3 mos	20,560	8,224	4,112
6 mos	4,925	1,970	985
12 mos	3,720	1,488	744
16 mos	2,863	1,145	573

*Risk shown as 1 per "X" troglitazone users

Population-Based Estimates of the Rate of Acute Liver failure with Troglitazone

Summary of Population Based Data on Risk of Acute Liver Failure with Troglitazone

Study	# Subjects	≥ 6 mos Rx	Person-yrs	Cases AHF	Absolute Risk per 10^3 persons	Incidence Rate per 10^6 pyrs (95% CI)
NDA	2510	45%	1426	0	0	0 (0-2584)
DPP	585	86%	580	1	1.7	1724 (44-9569)
REACH	2433	17% est	785	1	0.4	1274 (32-7077)

Reporting Rates of Acute Liver Failure with Troglitazone Over Time

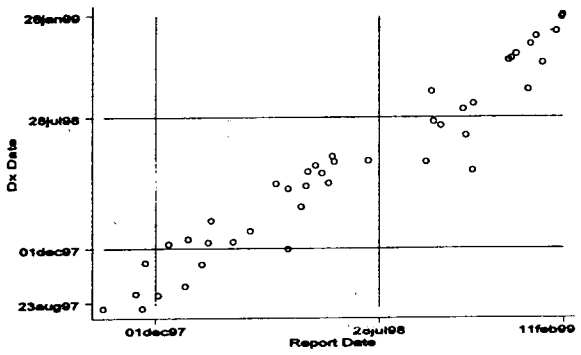
Effect of Time on Reporting of Cases of Acute Liver Failure with Troglitazone

Period	No. Started	Report Lag (d) Median (Range)	Duration of Use (d) Median (Range
Mar – Nov 97	22	62 (6-197)	153 (22-478)
Dec 97 – Jul 98	14	67 (9-126)	117 (4-225)
Aug 98 – Jan 99	7	32 (14-36)	30 (17-62)

Examination of Reporting Rates by Time Period

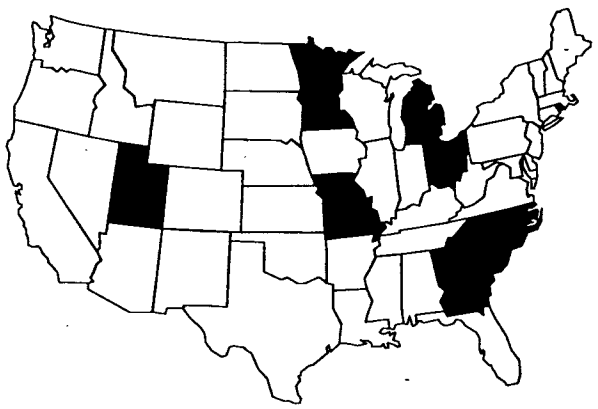
Period	No. Cases Started in Interval	No. Pts. in Interval	Reporting Rate per 10^5 Persons
Mar – Nov 97	22	459,800	4.78
Dec 97 – Jul 98	14	593,038	2.36
Aug 98 – Jan 99	7	253,412	2.76

Report Date by Date of Diagnosis



Study of Liver Enzyme Monitoring and Severe Liver Injury in Patients Treated with Troglitzone from the United HealthCare Database

United HealthCare Research Database Sites



Criteria for Inclusion in the Troglitazone Study Cohort of Liver Enzyme Monitoring

- Enrollment Date ≥ 90 days prior to 1st troglitazone prescription
- Disenrollment or end of study interval occurring prior to anticipated testing time

Size of Troglitazone Monitoring Study Cohort, UHC

Ever received troglitazone	9,369
Total person-years	4,873
≥ 90 day prior enrollment	7,568
Included in enzyme monitoring study	6,541

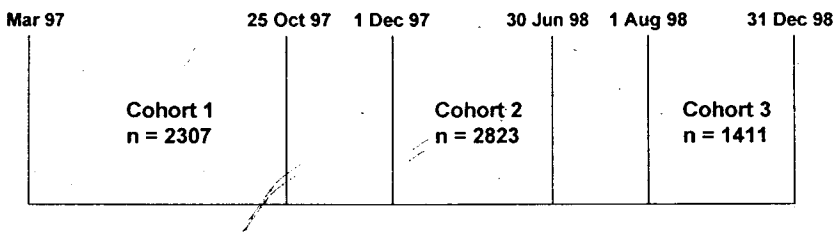
Timing Definitions and Outcome Measures for Liver Enzyme Monitoring Among Troglitazone Users in UHC

Baseline	-30 to +7 days from 1st troglitazone Rx
Monthly	± 7 days from 30 day anniversary date of 1st R
Included tests	Tests specifically including ALT or AST Multichannel tests (12-22) Nonspecific Hospital Revenue Codes for general and chemistry laboratory
Excluded tests	Isolated tests for albumin, total or direct bilirubin, LDH, alkaline phosphatase

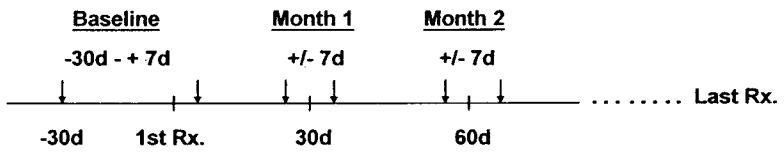
Troglitazone Labeling Regarding Liver Enzyme Monitoring Over Time

Mar-30Oct97	No liver enzyme monitoring recommendations
31Oct97-30Nov97	Monitor liver enzymes within first 1-2 mos of starting troglitazone; then every 3 mos first year; then periodically
1Dec97-27Jul98	Monitor at baseline; monthly x 6; every other month x3; then periodically
28Jul98-Present	Monitor at baseline; monthly x 8; every two months x 2; then periodically

Overview of Study of Liver Enzyme Monitoring in Troglitazone Users within the United HealthCare Database



Study Design for Measuring Occurrence of Liver Enzyme Monitoring



Liver Enzyme Testing in the Period 30 Days Prior to 7 Days after the First Troglitazone Prescription, by Time Period, UHC

	% with Baseline Test
Cohort 1 (n=2307)	24.5
Cohort 2 (n=2823)	37.0
Cohort 3 (n=1411)	45.1

Monthly Liver Enzyme Monitoring (+/-7d) by Time Period Among Troglitazone Users, UHC

	Month*					
	1	2	3	4	5	6
Cohort 1	5.5	7.0	7.1	4.3	3.1	7.4
Cohort 2	14.6	12.9	13.1	12.7	13.1	9.6
Cohort 3	17.3	14.5	14.0	10.4	0	

*Data Shown as Percentage of Eligible Subjects at Each Time Period

Monthly Liver Enzyme Monitoring (± 14d) by Time Period Among Troglitazone Users, UHC

	Month*					
	1	2	3	4	5	6
Cohort 1	9.1	11.6	10.8	9.7	7.5	12.6
Cohort 2	22.9	21.3	21.7	19.8	21.2	14.6
Cohort 3	26.1	25.2	23.3	18.7	0	

*Data Shown as Percentage of Eligible Subjects at Each Time Period

Sequential Liver Enzyme Monitoring Among Troglitazone Users, by Time Period, UHC

	Total Months of Troglitazone Use*					
	1	2	3	4	5	6
Cohort 1	10.5	2.8	0	0	0	0
Cohort 2	20.0	8.2	0	0	0	0
Cohort 3	22.3	10.4	0	0	0	0

*Data Shown as Percent of Eligible Subjects

Concomitant Anti-Diabetic Drug Use Among Troglitazone Users in UHC, No Enrollment Criteria, n = 9369

	Troglitazone Use and:					
	Troglit	Insulin	SU	Met	Acarbose	Other
Troglit	12.3%					
Insulin		27.7%	7.7%	4.5%	0.4%	
SU			23.5%	13.9%	0.7%	
Met					0.05%	
Acarbose					0.2%	
Other						5.2%

Trends in Concomitant Anti-Diabetic Drug Use Among Troglitazone Users in UHC, No Enrollment Criteria, n = 9369

	Troglitazone Monotherapy
Cohort 1 (n = 2585)	7.7%
Cohort 2 (n = 3688)	11.6%
Cohort 3 (n = 1875)	19.5%

Summary of Possible Cases of Severe Liver Injury in Patients Treated with Troglitzone, UHC*

Possible Acute Liver Failure

44 M	Liver transplant
85 M	Hepatic coma; undetermined outcome
62 F	Acute hepatic necrosis; undetermined outcome

Possible Hospitalized Drug-Induced Hepatitis

47 M	Increased transaminases
44 F	Drug-induced hepatitis; liver biopsy
67 F	Jaundice
55 M	Jaundice; acute renal failure; CHF

*Medical record review pending

Potential Incidence Rates of Severe Liver Injury in Troglitazone Users, UHC

	n	Incidence Rate per 10^6 pyrs (95% CI)
Possible Acute Liver Failure	3	616 (127-1798)
	2	410 (50-1482)
Possible Hepatitis	4	821 (224-2100)
	3	616 (127-1798)
Total	7	1437 (578-2957)
	5	1026 (333-2393)

Conclusions and Public Health Implications

Will be discussed

PDR® entry for
Rezulin Tablets (PARKE-DAVIS)

WARNINGS

Hepatic

Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities).

It is recommended that serum transaminase levels be checked at the start of therapy, monthly for the first six months of therapy, every two months for the remainder of the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT>3 times the upper limit of normal) and should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT>3 times the upper limit of normal).

DESCRIPTION

Rezulin® (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Rezulin is used in the management of type II diabetes (noninsulin-dependent diabetes mellitis (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (±-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, or the (alpha)-glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 stereoisomers having similar pharmacologic effects. The structural formula is as shown:

<Picture>

Troglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. Troglitazone has a molecular formula of C24H27NO8S and a molecular weight of 441.55 daltons. It is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrite, anhydrous ethanol, or ether; and practically insoluble in water.

Rezulin is available as 200, 300 and 400 mg tablets for oral administration formulated with the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80. povidone, purified water, silicon dioxide, titanium dioxide, and synthetic iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin. It has a unique mechanism of action that is dependent on the presence of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve binding to nuclear receptors (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, troglitazone is not an insulin secretagogue.

In animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type II diabetes. Plasma lactate and ketone body formation are also decreased. The metabolic changes produced by troglitazone result from the increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance. Treatment with troglitazone did not affect pancreatic weight, islet number or glucagon content, but did increase regranulation of the pancreatic beta cells in rodent models of insulin resistance.

Since troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (±1 SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	Cmax (µg/mL)	AUC (0-24) (µg-hr/mL)	CL/F * (mL/min)
200	0.90 (0.36)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

*CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (tmax) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [14C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400 mg dose of [14C]troglitazone after 14 days of treatment with 400 mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Studies in human microsomes suggest that Metabolite 3 is not subject to further metabolism by the major P450 isozymes. Troglitazone did not inhibit any of the major P450 enzymes at clinically relevent concentrations. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

The results of human in vivo drug interaction trials suggest that troglitazone induces cytochrome P450 3A4 at clinically relevent doses (see Drug Interactions).

Excretion: Following oral administration of [14C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. However, Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT>3 times the upper limit of normal); see WARNINGS).

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular

responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A1C. Unlike sulfonylureas, Rezulin does not stimulate insulin secretion. Addition of Rezulin to a sulfonylurea has a synergistic effect since both agents act to improve glucose tolerance by different but complementary mechanisms. These effects occur without weight loss and persist for 52 weeks of Rezulin treatment.

In clinical trials of Rezulin as monotherapy or in combination, an increase in LDL (up to 13%), HDL (up to 16%), and total cholesterol (total-C) (up to 5%) occurred while total-C/HDL and LDL/HDL ratios did not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Patients treated with Rezulin as monotherapy or in combination with other agents exhibited a reduction in fasting (-13% to -26%) and postprandial triglyceride levels. For patients on Rezulin and insulin, reduction in insulin doses may occur following Rezulin therapy and some attenuation of the triglyceride reduction may occur.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Rezulin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Rezulin does not stimulate insulin secretion, hypoglycemia in patients treated with Rezulin alone is not to be expected. Because of this insulin-dependent mechanism of action, Rezulin should not be used in patients with type I diabetes.

Clinical Studies

Combination With Sulfonylureas

A 52-week, double-blind, placebo-controlled study of Rezulin and 12 mg micronized glyburide, alone and in combination, was conducted in patients with type II diabetes (N=552), who had failed to achieve adequate glycemic control (FSG of 224 mg/dL and HbA1C of 9.6%) while on maximal doses of a sulfonylurea. Patients randomized to receive micronized glyburide showed mean increases in FSG and HbA1C.

TABLE 2. Combination Therapy With Glyburide: Mean Difference From 12 mg Micronized Glyburide Monotherapy (1 yr)

	200 mg	400 mg	600 mg	Rezulin + Glyburide	Rezulin + Glyburide	Rezulin + Glyburide	Glyburide	Glyburide
FSG (mg/dL)	Mean Baseline	226	231	220	Adjusted Mean Change From Baseline	-31	-38	-56
	Adjusted Mean Difference	-54 **	-61 **	-79 **	From Glyburide			
HbA1C(%)	Mean Baseline	9.5	9.7	9.5	Adjusted Mean Change From Baseline	-0.7	-0.9	-1.8
	Adjusted Mean Difference	-1.6 **	-1.8 **	-2.7 **	From Glyburide			
Insulin (μU/mL)	Mean Baseline	28.2	24.9	26.4	Adjusted Mean Change From Baseline	-3.8	-5.9	-6.1
	Adjusted Mean Difference	-2.4	-4.4 *	-4.6 *	From Glyburide			

*p <0.05 compared to continuation of glyburide monotherapy. **p <0.0001 compared to continuation of glyburide monotherapy.

TABLE 3. Combination Therapy With Glyburide:
Percent of Patients Achieving Glycemic Control At End of Study (1 yr)

Rezulin (mg)	0	200	400	600
Glyburide(mg)	12	12	12	12
HbA1C (%)				
</=7%	1	22	21	41
</=8%	10	33	33	60

A combination of 200, 400, or 600 mg of Rezulin with micronized glyburide achieved lower levels of fasting plasma glucose and HbA1C levels than either agent achieved alone (see Tables 2 and 3). These improvements in glycemic control were associated with mean weight gains of 5.8 to 13.1 pounds. To eliminate weight as a confounding factor in this study, patients had been instructed to follow a diet to maintain current weight.

Combination With Insulin

Two clinical studies were conducted to evaluate the effects of Rezulin on glycemic control and insulin dose in patients with type II diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA1C of 9.42 (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce the insulin doses only if two consecutive FSGs were </=100 mg/dL. Rezulin-treated patients showed a significant ($p<0.0001$) reduction in HbA1C compared with patients who received placebo (see Table 4).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA1C value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p<0.0001$) decrease in exogenous insulin dosage of 15% in the 200 mg Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA1C values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 4. Combination Therapy with Insulin: Mean Change From Baseline at 6 Months

	Troglitazone		
Parameter	Placebo	200 mg	600 mg
N	118	116	116
HbA1c(%)			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Mean Change From Baseline (SE)1	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference From Placebo (SE)	--	-0.72 (0.14) *	-1.29 (0.14) *
Percent Mean Change From Baseline	-1.3	-8.8	-15.1
Insulin daily dosage (units)			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change From Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference From Placebo (SE)	--	-12 (3.0) *	-30 (3.0) *
Percent Mean Change From Baseline	1	-15	-42 *

p </=0.0001 1Least squares mean adjusted for investigator center and baseline

<Picture>

<Picture>

A second 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose.

Patients treated with 200 mg (N=75) and 400 mg (N=76). Rezulin had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N=71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400 mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400 mg Rezulin group compared to 7% in the 200 mg group and 1.5% in the placebo group.

A greater than 50% reduction in insulin was achieved by 51% of patients on 200 mg and 70% on 400 mg once daily as compared to 17% on placebo.

Monotherapy

Three clinical trials, including 2 placebo-controlled studies with durations from 12 to 26 weeks have been conducted to study the use of Rezulin as monotherapy. These studies have examined Rezulin doses from 100 to 600 mg/day in approximately 1500 patients. The patients studied have included patients previously treated with a sulfonylurea who were studied following prior therapy wash out (N=1265) and patients previously treated with diet only (N=230). In patients previously treated with a sulfonylurea, Rezulin treatment did not result in an improvement in glycemic control beyond that seen with the patients' prior therapy, although glucose lowering was significantly better than that seen with placebo treatment. For patients previously treated with diet, Rezulin doses of 200 mg, 400 mg and 600 mg/day were associated with improved FSG compared to placebo. However, only the 600 mg/day dose resulted in a difference compared with placebo that was statistically significant in both studies (see Table 5). At 600 mg per day, 58% of patients previously treated with diet in the 12-week study and 47% of patients previously treated with diet in the 26-week study (versus placebo values of 28% and 21%, respectively) had a response to Rezulin of >/= 30 mg/dL reduction from baseline in fasting serum glucose.

TABLE 5. Glycemic Parameters in Diet-Failure Patients

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12 Week Study

Placebo 200 400 600

N 19 23 20 23 FSG (mg/dL) Mean Baseline 168 169 181 196 Adjusted Mean Change From Baseline 14 -14 -20 -38 Adjusted Mean Difference From Placebo -31* -37* -55* HbA1c(%) Mean Baseline 8 8.2 8.6 8.6 Adjusted Mean Change From Baseline -0.1 -0.6 -0.6 -0.8 Adjusted Mean Difference From Placebo -0.5 -0.6 -0.7 * 26 Week Study

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Placebo 200 400 600

N 18 18 19 15 FSG (mg/dL) Mean Baseline 202 191 201 201 Adjusted Mean Change From Baseline -6 -24 -17 -48 Adjusted Mean Difference From

Placebo -18 -10 -42* HbA1c(%) Mean Baseline 8.7 8.3 8.5 8.6 Adjusted Mean Change From Baseline 0.4 -0.2 0.3 -1 Adjusted Mean Difference From Placebo -0.6 -0.1 -1.4 *

---

*p<0.05

INDICATIONS AND USAGE

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Rezulin, as monotherapy, is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION). Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection of poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

WARNINGS

SEE BOXED WARNING.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hypoglycemia: Patients receiving Rezulin in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of concomitant agent may be necessary.

Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. These patients may be at risk for pregnancy.

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite at the 400 mg dose did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, Rezulin is not indicated unless the expected benefit is believed to outweigh the potential risk to patients with NYHA Class III or IV cardiac status.

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

Drug Interactions

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Terfenadine: Coadministration of Rezulin with terfenadine decreases the plasma concentration of both terfenadine and its active metabolite by 50-70% and may result in decreased efficacy of terfenadine.

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Glyburide: Coadministration of Rezulin and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics:

Digoxin: Coadministration of Rezulin with digoxin does not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of altered safety and efficacy should be considered when Rezulin is used concomitantly with these drugs.

Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. No tumors of any type were increased at the low and mid doses. Plasma drug exposure based on AUC of parent compound and total metabolites at the low and mid doses was up to 24-fold higher than human exposure at 400 mg daily. The highest dose in each sex exceeded the maximum tolerated dose. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose associated with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound and total metabolites that were at least 2-fold higher than the human exposures at 400 mg daily. No tumors of any type were

increased in mice at 50 mg/kg at exposures up to 40% of that in humans at 400 mg daily, based on AUC of parent compound and total metabolites.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an in vitro Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative was an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.

Animal Toxicology

Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible in 2- and 13-week studies, were prevented by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats but not mice. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. The incidence of these changes in drug-treated rats was increased compared to controls at twice the AUC of the 400 mg human dose.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures in rats (parent compound) and rabbits (parent compound and active metabolite) based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are associated with hepatic dysfunction or hepatitis have been reported, including: nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, abnormal liver function tests (including increased ALT, AST, LDH, alkaline phosphatase, bilirubin). Also see WARNINGS.

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 6. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 6. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 6. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency >/= 5% of Rezulin-Treated Patients % of Patients

---

Placebo Rezulin Placebo Rezulin N = 492 N = 1450 N = 492 N = 1450

Infection 22 18 Nausea 4 6 Headache 11 11 Rhinitis 7 5 Pain 14 10 Diarrhea 6 5 Accidental Injury 6 8 Urinary Tract Infection 6 5 Asthenia 5 6 Peripheral Edema 5 5 Dizziness 5 6 Pharyngitis 4 5 Back Pain 4 6

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with

Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see WARNINGS).

Postintroduction Reports

Adverse events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which causal relationship to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increased CPK and creatinine, hyperglycemia, syncope, anemia, malaise.

DOSAGE AND ADMINISTRATION

Rezulin should be taken with a meal.

Combination Therapy

Sulfonylureas: Rezulin in combination with a sulfonylurea should be initiated at 200 mg once daily. The current sulfonylurea dose should be continued upon initiation of Rezulin therapy. For patients not responding adequately, the Rezulin dose should be increased at 2 to 4 weeks. The maximum recommended dose is 600 mg once daily. The dose of sulfonylurea may require lowering to optimize therapy.

Insulin: The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response.

Monotherapy

Rezulin monotherapy in patients not adequately controlled with diet alone should be initiated at 400 or 600 mg once daily. For patients not responding to 400 mg once daily, the Rezulin dose should be increased to 600 mg after 6-8 weeks. For patients not responding adequately to 600 mg after 6-8 weeks, Rezulin should be discontinued and alternative therapeutic options should be pursued. See CLINICAL PHARMACOLOGY, Clinical Studies, Monotherapy.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism). Out of 2938 patients, 148 (5%) had a serum creatinine >/= 1.5 at baseline. Of these 148 patients, 145 had creatinine levels between 1.5 and 2.0, inclusive; only 3 patients had levels >2.0. No consistent trend was seen in any of these adverse events, and no worsening of renal insufficiency was observed.

Patients With Hepatic Impairment

Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT>3 times the upper limit of normal). See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency, and WARNINGS.

HOW SUPPLIED

Rezulin is available in 200, 300 and 400 mg tablets as follows:

200 mg Tablets: Yellow, oval, non-scored, film-coated tablet with "PD 352" debossed on one side, and "200" on the other, available in:

N 0071-0352-15 Bottles of 30

N 0071-0352-23 Bottles of 90

N 0071-0352-40 (10 × 10 unit-dose blisters)

300 mg Tablets: White, oval, non-scored, film-coated tablet with "PD 357" debossed on one side and "300" on the other, available in:

N 0071-0357-20 Bottles of 60

N 0071-0357-25 Bottles of 120

400 mg Tablets: Tan, oval, non-scored, film-coated tablet with "PD 353" debossed on one side, and "400" on the other, available in:

N 0071-0353-15 Bottles of 30

N 0071-0353-23 Bottles of 90

N 0071-0353-40 (10 × 10 unit-dose blisters)

Storage

Store at controlled room temperature 20°C-25°C (68°-77°F). Protect from moisture and humidity.

Rx only

February 1998

Manufactured by:

Parke Davis Pharmaceuticals, Ltd.

Vega Baja, PR 00694

Distributed by

PARKE-DAVIS

Div of Warner-Lambert Co

Morris Plains, NJ 07950 USA

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Rezulin®
(Troglitazone) Tablets

WARNINGS

Hepatic

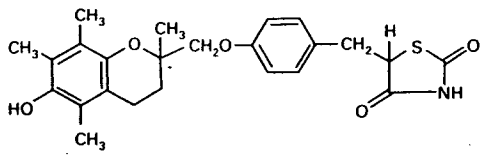
Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. (See ADVERSE REACTIONS, Laboratory Abnormalities.)

Serum transaminase levels should be checked at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter. Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT>1.5 times the upper limit of normal). Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. If serum transaminase levels are moderately increased (ALT>1.5 to 2 times the upper limit of normal), liver function tests should be repeated within a week and then weekly until the levels return to normal. If at any time a patient has jaundice or ALT rises above 3 times the upper limit of normal, Rezulin should be discontinued.

ESCRIPTION

ezulin® (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing sulin resistance. Rezulin is used in the management of type II diabetes (noninsulin-dependent abetes mellitus (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (±-5-[[4-[(3,4-ydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazo-inedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, th glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 e ers having similar pharmacologic effects. The structural formula is as shown:



oglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. oglitazone has a molecular formula of $C_{24}H_{27}NO_5S$ and a molecular weight of 441.55 daltons. is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrile, anhydrous ethanol, or ether; and practically insoluble in water.

ezulin is available as 200, 300 and 400 mg tablets for oral administration formulated with the llowing excipients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium earate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, povidone, purified ater, silicon dioxide, titanium dioxide, and synthetic iron oxides.

LINICAL PHARMACOLOGY

echanism of Action

oglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving tar-t cell response to insulin. It has a unique mechanism of action that is dependent on the pres-ice of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-pendent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve nding to nuclear receptors (PPAR) that regulate the transcription of a number of insulin sponsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, oglitazone is not an insulin secretagogue.

animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and pertriglyceridemia characteristic of insulin-resistant states such as type II diabetes. Plasma state and ketone body formation are also decreased. The metabolic changes produced by oglitazone result from the increased responsiveness of insulin-dependent tissues and are served in numerous animal models of insulin resistance. Treatment with troglitazone did not ect pancreatic weight, islet number or glucagon content, but did increase regranulation of the ncreatic beta cells in rodent models of insulin resistance.

nce troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it es not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Rezulin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Rezulin does not stimulate insulin secretion, hypoglycemia in patients treated with Rezulin alone is not to be expected. Because of this insulin-dependent mechanism of action, Rezulin should not be used in patients with type I diabetes.

Clinical Studies

Combination With Sulfonylureas

A 52-week, double-blind, placebo-controlled study of Rezulin and 12 mg micronized glyburide, alone and in combination, was conducted in patients with type II diabetes (N=552), who had failed to achieve adequate glycemic control (FSG of 224 mg/dL and HbA_{1C} of 9.6%) while on maximal doses of a sulfonylurea. Patients randomized to receive micronized glyburide showed mean increases in FSG and HbA_{1C}. Similarly, patients who switched from a sulfonylurea to Rezulin monotherapy also demonstrated increases in FSG and HbA_{1C}.

TABLE 2. Combination Therapy With Glyburide: Mean Difference From 12 mg Micronized Glyburide Monotherapy (1 yr)

	200 mg Rezulin + Glyburide	400 mg Rezulin + Glyburide	600 mg Rezulin + Glyburide
FSG (mg/dL)			
Mean Baseline	226	231	220
Adjusted Mean Change From Baseline	-31	-38	-56
Adjusted Mean Difference From Glyburide	-54**	-61**	-79**
HbA_{1C} (%)			
Mean Baseline	9.5	9.7	9.5
Adjusted Mean Change From Baseline	-0.7	-0.9	-1.8
Adjusted Mean Difference From Glyburide	-1.6**	-1.8**	-2.7**
Insulin (µU/mL)			
Mean Baseline	28.2	24.9	26.4
Adjusted Mean Change From Baseline	-3.8	-5.9	-6.1
Adjusted Mean Difference From Glyburide	-2.4	-4.4*	-4.6*

* $p < 0.05$ compared to continuation of glyburide monotherapy.
** $p < 0.0001$ compared to continuation of glyburide monotherapy.

TABLE 3. Combination Therapy With Glyburide: Percent of Patients Achieving Glycemic Control at End of Study (1 yr)

Rezulin (mg)	0	200	400	600
Glyburide (mg)	12	12	12	12
HbA_{1C} (%)				
≤7%	1	22	21	41
≤8%	10	33	33	60

A combination of 200, 400, or 600 mg of Rezulin with micronized glyburide achieved lower levels of fasting plasma glucose and HbA_{1C} levels than either agent achieved alone (see Tables 2 and 3). These improvements in glycemic control were associated with mean weight gains of 5.8 to 13.1 pounds. To eliminate weight as a confounding factor in this study, patients had been instructed to follow a diet to maintain current weight.

Combination With Insulin

Two clinical studies were conducted to evaluate the effects of Rezulin on glycemic control and insulin dose in patients with type II diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1C} of 9.42 (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were ≤100 mg/dL. Rezulin-treated patients showed a significant ($p<0.0001$) reduction in HbA_{1C} compared with patients who received placebo (see Table 4).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1C} value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p<0.0001$) decrease in exogenous insulin dosage of 15% in the 200 mg Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA_{1C} values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 4. Combination Therapy with Insulin: Mean Change From Baseline at 6 Months

Parameter	Placebo	Troglitazone 200 mg	Troglitazone 600 mg
N	118	116	116
HbA_{1C} (%)			

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (±1 SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	Cmax (µg/mL)	AUC (0-24) (µg·hr/mL)	CL/F* (mL/min)
200	0.90 (0.36)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

*CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (tmax) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [^{14}C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400 mg dose of [^{14}C]troglitazone after 14 days of treatment with 400 mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Studies in human microsomes suggest that Metabolite 3 is not subject to further metabolism by the major P450 isozymes. Troglitazone did not inhibit any of the major P450 enzymes at clinically relevant concentrations. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

The results of human *in vivo* drug interaction trials suggest that troglitazone induces cytochrome P450 3A4 at clinically relevant doses (see Drug Interactions).

Excretion: Following oral administration of [^{14}C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. However, Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT>1.5 times the upper limit of normal); see WARNINGS.

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1C}. Unlike sulfonylureas, Rezulin does not stimulate insulin secretion. Addition of Rezulin to a sulfonylurea has a synergistic effect since both agents act to improve glucose tolerance by different but complementary mechanisms. These effects occur without weight loss and persist for 52 weeks of Rezulin treatment.

In clinical trials of Rezulin as monotherapy or in combination, an increase in LDL (up to 13%), HDL (up to 16%), and total cholesterol (total-C) (up to 5%) occurred while total-C/HDL and LDL/HDL ratios did not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Patients treated with Rezulin as monotherapy or in combination with other agents exhibited a reduction in fasting (-13% to -26%) and postprandial triglyceride levels. For patients on Rezulin and insulin, reduction in insulin doses may occur following Rezulin therapy and some attenuation of the triglyceride reduction may occur.

PARKE-DAVIS

Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.10)
Mean Change From Baseline (SE)[1]	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference From Placebo (SE)	--	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change From Baseline	-1.3	-8.8	-15.1
Insulin daily dosage (units)			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change From Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference From Placebo (SE)	--	-12 (3.0)*	-30 (3.0)*
Percent Mean Change From Baseline	1	-15	-42

* $p \leq 0.0001$

[1]Least squares mean adjusted for investigator center and baseline

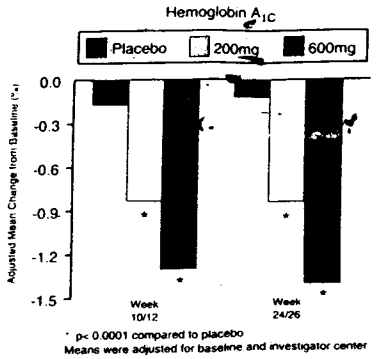


FIGURE 1: Combination Therapy With Insulin, Mean Change From Baseline for HbA_{1C}

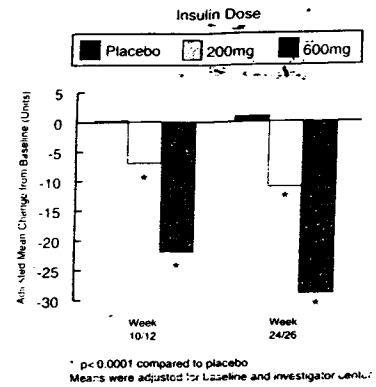


FIGURE 2: Combination Therapy With Insulin, Mean Change From Baseline for Insulin Dose

A second 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose.

Patients treated with 200 mg (N=75) and 400 mg (N=76) Rezulin had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N=71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400 mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400 mg Rezulin group compared to 7% in the 200 mg group and 1.5% in the placebo group.

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A greater than 50°₀ reduction in insulin dose was achieved by 51°₀ of patients on 200 mg and 70°₀ on 400 mg once daily as compared to 17°₀ on placebo.

Monotherapy

Clinical trials, including 2 placebo-controlled studies with durations from 12 to 26 weeks, were conducted to study the use of Rezulin as monotherapy. These studies have examined Rezulin doses from 100 to 600 mg/day in approximately 1500 patients. The patients studied have included patients previously treated with a sulfonylurea who were studied following prior therapy wash out (N=1265) and patients previously treated with diet only (N=230). In patients previously treated with a sulfonylurea, Rezulin treatment did not result in an improvement in glycemic control beyond that seen with the patients' prior therapy, although glucose lowering was significantly better than that seen with placebo treatment. For patients previously treated with diet, Rezulin doses of 200 mg, 400 mg and 600 mg/day were associated with improved FSG compared to placebo. However, only the 600 mg/day dose resulted in a difference compared with placebo that was statistically significant in both studies (see Table 5). At 600 mg per day, 58% of patients previously treated with diet in the 12-week study and 47% of patients previously treated with diet in the 26-week study (versus placebo values of 28% and 21%, respectively) had a response to Rezulin of ≥ 30 mg/dL reduction from baseline in fasting serum glucose.

TABLE 5. Glycemic Parameters in Diet-Failure Patients

	12 Week Study			
	Placebo	200	400	600
N	19	23	20	33
FSG (mg/dL)				
Mean Baseline	168	169	181	196
Adjusted Mean Change From Baseline	14	-14	-20	-38
Adjusted Mean Difference From Placebo		-31*	-37*	-55*
HbA_{1c} (%)				
Mean Baseline	8	8.2	8.6	8.6
Adjusted Mean Change From Baseline	-0.1	-0.6	-0.6	-0.8
Adjusted Mean Difference From Placebo		-0.5	-0.6	-0.7*
	26 Week Study			
	Placebo	200	400	600
N	18	18	19	15
FSG (mg/dL)				
Mean Baseline	202	191	201	201
Adjusted Mean Change From Baseline	-6	-24	-17	-48
Adjusted Mean Difference From Placebo		-18	-10	-42*
HbA_{1c} (%)				
Mean Baseline	8.7	8.3	8.5	8.6
Adjusted Mean Change From Baseline	0.4	-0.2	0.3	-1
Adjusted Mean Difference From Placebo		-0.6	-0.1	-1.4*

*$p<0.05$

INDICATIONS AND USAGE

Rezulin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control.

Rezulin monotherapy is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes (see DOSAGE AND ADMINISTRATION). Rezulin should not be used as monotherapy in patients previously well-controlled on sulfonylurea therapy. For patients inadequately controlled with a sulfonylurea alone, Rezulin should be added to, not substituted for, the sulfonylurea.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

WARNINGS

SEE BOXED WARNING.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hypoglycemia: Patients receiving Rezulin in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These

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changes associated with AUC values of parent compound and total metabolites that were at least 2-fold higher than the human exposure at 400 mg daily. No tumors of any type were increased in mice at 50 mg/kg at exposures up to 40°₀ of that in humans at 400 mg daily, based on AUC of parent compound and total metabolites.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC of parent compound at these doses was estimated to be 3- to 9-fold higher than the human exposure.

Animal Toxicology

Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day. These heart weight increases were reversible in 2- and 13-week studies, were prevented by coadministration of an ACE inhibitor, and 14 days of troglitazone administration to rats did not affect left ventricular performance. In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats but not in mice. In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of myocytes. The incidence of these changes in drug-treated rats was increased compared to controls at twice the AUC of the 400 mg human dose.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures in rats (parent compound) and rabbits (parent compound and active metabolite) based on AUC at these doses were up to 9-fold and 3-fold higher, respectively. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Two patients in the clinical studies developed reversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction. An additional patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. Symptoms that are associated with hepatic dysfunction or hepatitis have been reported, including: nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, abnormal liver function tests (including increased ALT, AST, LDH, alkaline phosphatase, bilirubin). Also see WARNINGS.

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 6. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 6. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 6. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients

	% of Patients			
	Placebo N = 492	Rezulin N = 1450	Placebo N = 492	Rezulin N = 1450
Infection	22	18	Nausea 4	6
Headache	11	11	Rhinitis 7	5
Pain	14	10	Diarrhea 6	5
Accidental Injury	6	8	Urinary Tract Infection 6	5
Asthenia	5	6	Peripheral Edema 5	5
Dizziness	5	6	Pharyngitis 4	5
Back Pain	4	6		

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology). Serial echocardiographic evaluations in monkeys treated chronically at exposures at 4-9 times the human exposure to parent compound and active metabolite at the 400 mg dose did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) has been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, Rezulin is not indicated unless the expected benefit is believed to outweigh the potential risk to patients with NYHA Class III or IV cardiac status.

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

Patients who develop nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or other symptoms suggestive of hepatic dysfunction or jaundice should immediately report these signs or symptoms to their physician. Patients should be informed that blood will be drawn to check their liver function at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

Drug Interactions

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Terfenadine: Coadministration of Rezulin with terfenadine decreases the plasma concentration of both terfenadine and its active metabolite by 50-70% and may result in decreased efficacy of terfenadine.

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Glyburide: Coadministration of Rezulin and glyburide does not appear to alter troglitazone or glyburide pharmacokinetics.

Digoxin: Coadministration of Rezulin with digoxin does not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. Studies have not been performed with other drugs metabolized by this enzyme such as: astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate. The possibility of altered safety and efficacy should be considered when Rezulin is used concomitantly with these drugs.

Patients stable on one or more of these agents when Rezulin is started should be closely monitored and their therapy adjusted as necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. No tumors of any type were increased at the low and mid doses. Plasma drug exposure based on AUC of parent compound and total metabolites at the low and mid doses was up to 24-fold higher than human exposure at 400 mg daily. The highest dose in each sex exceeded the maximum tolerated dose. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose associated with increased tumor incidence (400 mg/kg) was asso-

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Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During all clinical studies in North America, a total of 48 of 2521 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal. During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see WARNINGS).

Postintroduction Reports

Adverse events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which causal relationship to drug has not been established include the following: congestive heart failure, weight gain, edema, fever, abnormal lab tests including increased CPK and creatinine, hyperglycemia, syncope, anemia, malaise.

DOSAGE AND ADMINISTRATION

Rezulin should be taken with a meal.

Combination Therapy

Sulfonylureas: Rezulin in combination with a sulfonylurea should be initiated at 200 mg once daily. The current sulfonylurea dose should be continued upon initiation of Rezulin therapy. For patients not responding adequately, the Rezulin dose should be increased at 2 to 4 weeks. The maximum recommended dose is 600 mg once daily. The dose of sulfonylurea may require lowering to optimize therapy.

Insulin: The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response.

Monotherapy

Rezulin monotherapy in patients not adequately controlled with diet alone should be initiated at 400 or 600 mg once daily. For patients not responding to 400 mg once daily, the Rezulin dose should be increased to 600 mg after one month. For patients not responding adequately to 600 mg after one month, Rezulin should be discontinued and alternative therapeutic options should be pursued. See CLINICAL PHARMACOLOGY, Clinical Studies, Monotherapy.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism). Out of 2938 patients, 148 (5%) had a serum creatinine ≥1.5 at baseline. Of these 148 patients, 145 had creatinine levels between 1.5 and 2.0, inclusive; only 3 patients had levels >2.0. No consistent trend was seen in any of these adverse events, and no worsening of renal insufficiency was observed.

Patients With Hepatic Impairment

Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT>1.5 times the upper limit of normal). See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency and WARNINGS.

HOW SUPPLIED

Rezulin is available in 200, 300 and 400 mg tablets as follows:

200 mg Tablets: Yellow, oval, non-scored, film-coated tablet with "PD 352" debossed on one side, and "200" on the other, available in:
N 0071-0352-15 Bottles of 30 N 0071-0352-23 Bottles of 90
N 0071-0352-40 (10 x 10 unit-dose blisters)

300 mg Tablets: White, oval, non-scored, film-coated tablet with "PD 357" debossed on one side and "300" on the other, available in:
N 0071-0357-20 Bottles of 60 N 0071-0357-25 Bottles of 120

400 mg Tablets: Tan, oval, non-scored, film-coated tablet with "PD 353" debossed on one side, and "400" on the other, available in:
N 0071-0353-15 Bottles of 30 N 0071-0353-23 Bottles of 90
N 0071-0353-40 (10 x 10 unit-dose blisters)

Storage

Store at controlled room temperature 20°C-25°C (68°F-77°F). Protect from moisture and humidity.

Rx only

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